

REMARKS

Claims 1-2 and 8-11 are presently pending in the captioned application. Subsequent to the enclosed amendment, claims 1-2 and 8-11 are currently amended. Claims 3-7 are cancelled without disclaimer or prejudice as to the subject matter contained therein.

Claims 1 and 8 have been amended to add the proper language directed to a Markush group of benzimidazole derivatives. Remaining claims 2 and 9-11 have been amended as to matters of form.

No new matter within the meaning of § 132 has been added by any of the amendments.

Additionally, Applicant submits herewith a § 1.132 declaration by the inventor Mr. Woo providing evidence of unexpected results of the presently claimed invention. The submitted § 1.132 declaration contains a statistical analysis of the unexpectedly superior results of the presently claimed invention. The evidence shows that a formulation coated with the presently claimed enteric coating results in an unexpectedly higher residual content than formulations coated outside the presently claimed range of phthalyl content of 21 to 27%.

Applicant also submits herewith two Certificate of Analysis for HMPCP-50 and HPMCP-55 by the manufacturer Shin-Etsu Chemical

Co., Ltd. The Certificate of Analysis clearly show that HP-50 has a phthalyl content of 21-27 within the claimed range while HP-55 has a phthalyl content of 27-35, which is outside the claimed range.

Accordingly, Applicant respectfully requests the Examiner to enter the indicated amendments of Appendix ^b and to reconsider and withdraw the rejections and allow all claims as presently claimed in this application.

1. Rejection of Claims 1-2, 9 and 11
under 35 U.S.C. § 112, ¶ 2 paragraph

The Office Action rejects claims 1-2, 9 and 11 under 35 U.S.C. § 112, ¶ 2 paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The Office Action states:

The claims are drawn toward a pharmaceutical formulation comprising a core of benzimidazole drug; said formulation having enteric coating wherein the coating agent is hydroxypropylmethylcellulose phthalate (HPMCP). According to the claims, the coating agent is on the surface of the core, has a degree of substitution by phthalic acid group of 20- 70% omeprazole or other benzimidazole.

The issue is (i) whether the core of the formulation is 100% omeprazole and the omeprazole is admixed with the coating agent wherein the omeprazole constitutes 20-70% of the enteric coating or (ii) where the

benzimidazole derivative is not omeprazole, whether the core of the formulation is made up of 100% of the specified benzimidazole (e.g. picoprazole) and the enteric coating is made up of 20-70% omeprazole or (iii) whether the core of the formulations is made up of 100% omeprazole and that the enteric coating comprises of the specified benzimidazole derivative.

Applicant is advised to clarify the claims in regards to the issues (i) to (iii) by specifying the exact benzimidazole derivative that forms the core of each formulation and the percent of what derivative of the benzimidazole that is present in the enteric coating.

The examiner is interpreting the claims as consistent with the meanings of the three possibilities as outlined under this section.

Applicants respectfully traverse the rejections because the claim clearly shows that the enteric coating is made of a hydroxypropyl methylcellulose phthalate having a degree of substitution by phthalic acid group of 20 to 27% and not any another combination as suggested by the Office Action. The presently claimed invention is directed to enteric coatings where the benzimidazole is formed into a complex with an anion-exchange resin formed into the core that is coated by the enteric coating.

However, Applicants in the interest of advancing prosecution have amended the claims to recite a Markush group of benzimidazole derivatives to more clearly show that the benzimidazole derivatives are not admixed with the enteric coating.

Accordingly, Applicant respectfully submits that the claims particularly point out and distinctly claim the subject matter of the presently claimed invention and request withdrawal of the rejections under § 112, ¶ 2.

**2. Rejection of Claims 1-2 and 8-11
under 35 U.S.C. § 103(a)**

The Office Action rejects claims 1-2 and 8-11 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 4,786,505 ("Lovgren et al.") in view of U.S. Patent No. 5,026,560 ("Makino et al.") further in view of U.S. Patent No. 3,336,192 ("Sarett et al."). The Office Action states:

The claims are drawn toward enteric coated formulation of a benzimidazole derivative comprising a core containing a complex of benzimidazole derivative and an ion exchange resin and enteric coating on the surface of the core. According to the claims, the enteric coating is hydroxypropylmethylcellulose phthalate (HPMCP) having a degree of substitution by phthalic acid group of 20-27% omeprazole, pantoprazole, timoprazole or picoprazole. The claims are also directed toward a method of preparing the formulation; said method comprising coating the core containing benzimidazole and ion-exchange resin with enteric coating agent (HPMCP) having a degree of substitution by phthalic acid group of 20-27% omeprazole, pantoprazole, timoprazole or picoprazole. The claims further specify the benzimidazole derivative---i.e. that the formulation comprises of pantoprazole, timoprazole or picoprazole.

Lovgren et al (Patent '505) disclose a pharmaceutical preparation comprising omeprazole as the core of the tablet formulation (col 11, lin 50); said formulation having enteric coating comprising of hydroxypropymethylcellulose phthalate (col 17, lin 15) and a process of preparation of the formulation (col 18, lin 15-20).

Patent '505 does not disclose the use of ion-exchange resin in combination with the benzimidazole in preparing the core of the formulation.

Makino et al (Patent '560) disclose spherical granules having a core comprising of benzimidazole derivatives and enteric coating (abstract, col 3, lin 25-40 and col 9, lin 20-50). According to Makino et al, the enteric coating of the formulation comprises of anionic acrylate copolymer-HPMCP (col 10, lin 50-55).

Sarett et al (Patent '192) disclose antihelmintic composition comprising benzimidazoles and a method of making the formulation (col 5, lin 35 and col 12, lin 10-40). Patent '192 discloses the use of a resins as ingredient for making the composition; pointing out that the resin and other active ingredients used in that formulation in that invention such as waxes, synthetic polymers when associated with the benzimidazole active ingredient maintains the ingredient in inert or inoperative form so long as the composition remains in the acidic stomach (col 6, lin 35-50).

One of ordinary skill in the art would have been motivated to prepare a pharmaceutical composition having benzimidazole and ion exchange resins as active ingredients and coat the formulation with enteric coating agent such as HPMP as per the disclosures in the cited prior art. One of ordinary skill in the art would expect that by incorporating the

drug into an enteric coating polymeric material such as HPMCP, one of ordinary skill would obtain a stabilized imiprazole formulation for delayed release targeting of the drug into the ileum and/or colon. In short, enteric coated omeprazole formulation can survive the acidic environment of the stomach and release the drug into the distal portions of the gastrointestinal tract where the pH is alkaline. The presence of acid is a prerequisite to the conversion of omeprazole to its chemically active form but the resulting active compound-sulfenamide is a labile molecule which transforms further to unreactive compounds. Hence, enterically coating the drug to resist the acid medium in the stomach is useful for obtaining the drug in active form for treatment of intestinal infections. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill at the time the invention was made.

Applicant respectfully traverses this rejection because a *prima facie* case of obviousness has not been established. Each and every one of the presently claimed limitations are not taught or suggested by the cited references. In particular, the cited references fail to teach a hydroxypropyl methylcellulose phthalate (HPMCP) having a degree of substitution ("D.S.") by phthalic acid of 20 to 27% used as an enteric coating for benzimidazole drug complexed with an anion-exchange resin as the core.

Even assuming *arguendo* that a *prima facie* case has been made out, Applicant rebuts the presumption with evidence contained in the submitted § 1.132 Declaration demonstrating that the presently

claimed degree of substitution ("D.S.") by phthalic acid of 20 to 27% unexpectedly results in an enteric coating having a higher residual content than omeprazole formulations coated with HPMCP having a D.S. by phthalic acid outside the presently claimed range.

Rule of Law

The Federal Circuit held that a *prima facie* case of obviousness must establish: (1) some suggestion or motivation to modify the references; (2) a reasonable expectation of success; and (3) that the prior art references teach or suggest all claim limitations. Amgen, Inc. v. Chugai Pharm. Co., 18 USPQ2d 1016, 1023 (Fed. Cir. 1991); In re Fine, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988); In re Wilson, 165 USPQ 494, 496 (C.C.P.A. 1970).

Even if a *prima facie* case of obviousness has been established, secondary considerations such as commercial success, long felt but unsolved need, failure of others, and unexpected results may nevertheless give rise to a patentable invention. Graham v. John Deere Co., 148 U.S.P.Q. 459 (1966). Where the claimed and prior art products are substantially similar, a *prima facie* case of obviousness can also be rebutted by demonstrating that the prior art products do not possess the characteristics of the claimed invention. In re Best, 196 U.S.P.Q. 430, 433 (C.C.P.A. 1977).

Amended claim 1

In the present application, amended independent claim 1 recites, an enteric coated formulation of a benzimidazole derivative, comprising

a core containing a complex of the benzimidazole derivative and an anion-exchange resin, and

an enteric coating on the surface of said core,

said enteric coating being hydroxypropyl methylcellulose phthalate having a degree of substitution by phthalic acid group of 20 to 27%, and said benzimidazole derivative being selected from the group consisting of omeprazole, pantoprazole, timoprazole or picoprazole.

The cited references do not teach all the claimed limitations

The references fail to teach or suggest that HPMCP having a D.S. by phthalic acid of 20 to 27% results in an enteric coating for benzimidazole derivative having unexpectedly higher residual content characteristics. Advantageously, the presently claimed enteric coating avoids the use of a water-soluble inner film for pharmaceutical formulations having benzimidazole as the active ingredient.

Lovgren et al. only teaches a pharmaceutical preparation comprising omeprazole as the core of the tablet formulation wherein

the formulation has an enteric coating comprising hydroxypropylmethylcellulose phthalate. However, nothing in the reference teaches or suggests the presently claimed degree of substitution by phthalic acid group of 20 to 27%.

Similarly, Makino et al. only discloses spherical granules having a core comprising benzimidazole derivatives and an enteric coating. Although Makino et al. teaches an enteric coating of the formulation being anionic acrylate copolymer-HPMCP, nothing in the reference teaches or suggests the presently claimed degree of substitution by phthalic acid group of 20 to 27%.

Sarett et al. teaches an anti-helminthic composition comprising benzimidazoles and a method of making the formulation and the use of resins as an ingredient for making the composition. Sarett et al. also points out that resin and other active ingredients used in the formulation such as waxes, synthetic polymers associated with the benzimidazole active ingredient maintains the ingredient in inert or inoperative form so long as the composition remains in the acidic stomach. But again, nothing in the reference relates to the degree of substitution by phthalic acid group of 20 to 27%.

In particular, orally-administered formulations of benzimidazole derivatives cannot be exposed to gastric juice due to the rapid degradation of benzimidazole in acidic environments. If the drug is prematurely exposed to stomach acids, the formulation

would degrade and fail to reach the intestine. In order to reduce the formulation's acid-labile properties, a stabilizing agent such as an alkaline ingredient is usually added.

However, the addition of the alkaline agent to the enteric coatings impairs the enteric coating which in turn reduces storage stability. Moreover, known methods require a water-soluble inner film which are unreliable and often result in inferior products which also have reduced stability. The lack of motivation to make the presently claimed invention is further evidenced by the unpredictable nature of pharmacokinetics.

Pharmacokinetics is an incredibly complex subject that is unique to each class of compound. Each pharmacokinetic study requires application of robust stochastic theory; population modeling; investigation of process and measurement noise; evaluation of alternative parameterizations of pharmacokinetic models; optimal monitoring strategies and finally clinical trials.

The unpredictable nature of pharmacokinetics and the unpredictable nature of shelf life for enteric coatings would make it extremely difficult for one of ordinary skill in the art to make the presently claimed limitation of HPMCP having a D.S. by phthalic acid of 20 to 27% without some suggestion or motivation. Clearly, in this case, one of ordinary skill would not have been provided with any guidance regarding all these various parameters

for a benzimidazole formulation having increased storage stability from the cited references.

Even assuming *arguendo* that a *prima facie* exists, the § 1.132 Declaration provides statistical evidence that the presently claimed enteric coating having a degree of substitution by a phthalic acid group of 20 to 27% (HMPCP-50) unexpectedly improves the shelf life of benzimidazole derivatives over enteric coatings having a substitution outside the claimed range such as HP-55 (27.0 to 35.0% as shown in Certificate of Analysis).

In particular, fifteen core tablets per formulation were prepared in accordance with the same procedures as Example 1 of the present specification. Samples 1 and 2 contain an omeprazole complex while Samples 3 and 4 contain a pantoprazole complex. Samples 1 and 3 have the coating composition with the ingredient HP-50 falling within the claimed limitations while Sample 2 and 4 have the coating composition with the ingredient HP-55 falling outside the presently claimed limitations.

The statistical grouped data of these fifteen core tablets shows that the presently claimed composition unexpectedly results in higher residual content having a degree of substitution by a phthalic acid group of 20 to 27%. As the court stated in In re Corkill, "a greater than expected result is an evidentiary factor pertinent to the legal conclusion of [non]obviousness". 711 F.2d

1496, 266 USPQ 1005 (Fed. Cir. 1985). The statistical analysis clearly shows that there is a reliable statistical basis for patentable distinctions between the prior art and the presently claimed formulations.

Accordingly, Applicant respectfully submits that the presently claimed invention is unobvious over the cited references and respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103.

3. Rejection of Claims 1-2 and 8-11
under 35 U.S.C. § 103(a)

The Office Action rejects claims 1-2 and 8-11 under 35 U.S.C. § 103(a), as being unpatentable over U.S. Patent No. 4,786,505 ("Lovgren et al.") in view of U.S. Patent No. 6,726,927, filed August 27, 1998 ("Chen et al.") further in view of U.S. Patent No. 3,324,102 ("Pierre et al."). The Office Action states:

The claims are as discussed in section one above.

The disclosures of Lovgren et al (Patent '505) are also discussed above.

Lovgren et al do not disclose the use of ion-exchange resin in combination with the benzimidazole in preparing the core of the formulation and Lovgren et al also do not disclose the use of other benzimidazole derivatives.

Chen et al (Patent '972) disclose enteric coated pharmaceutical dosage forms containing omeprazole or lansoprazole as the core ingredient and the process or method for their manufacture (abstract and col 10, lin 15-40).

Chen et al do not disclose the use of any other benzimidazole derivatives in the formulations.

Pierre et al (Patent '102) disclose water-soluble benzimidazole-containing compositions and methods for making the compositions having several derivatives as active ingredients. More importantly, Patent '102 discloses that enteric vehicles and compositions are particularly useful for treatment of animals suffering from severe helminthic infections of the intestinal tract and that the enteric property can be imparted to the formulation by coating said formulations with enteric coatings containing resins, waxes, synthetic polymers; etc.

One of ordinary skill in the art would have been motivated to prepare a pharmaceutical composition having benzimidazole and ion exchange resins as active ingredients and coat the formulation with enteric coating agent such as HPMP as per the disclosures in the cited prior art. One of ordinary skill in the art would expect that by incorporating the drug into an enteric coating polymeric material such as HPMCP, one of ordinary skill would obtain a stabilized imiprazole formulation for delayed release targeting of the drug into the ileum and/or colon. In short, enteric coated omeprazole formulation can survive the acidic environment of the stomach and release the drug into the distal portions of the gastrointestinal tract where the pH is alkaline.

The presence of acid is a prerequisite to the conversion of omeprazole to its chemically active form but the resulting active compound-

sulfenamide is a labile molecule which transforms further to unreactive compounds. Hence, enterically coating the drug to resist the acid medium in the stomach is useful for obtaining the drug in active form for treatment of intestinal infections.

Furthermore, in view of the use of derivatives of benzimidazole in formulations by Pierre et al (Patent '102), one of ordinary skill would be have expected reasonable success in substituting one derivative for the other in making the formulations, as in the instant claims.

Applicant respectfully traverses this rejection because a *prima facie* case of obviousness has not been established. Each and every one of the presently claimed limitations are not taught or suggested by the cited references. In particular, the cited references fail to teach a hydroxypropyl methylcellulose phthalate (HPMCP) having a degree of substitution ("D.S.") by phthalic acid of 20 to 27% used as an enteric coating for benzimidazole drug complexed with an anion-exchange resin as the core.

Even assuming *arguendo* that a *prima facie* case has been made out, Applicant rebuts the presumption with evidence contained in the submitted § 1.132 Declaration demonstrating that the presently claimed degree of substitution ("D.S.") by phthalic acid of 20 to 27% unexpectedly results in an enteric coating having a higher residual content than omeprazole formulations coated with HPMCP having a D.S. by phthalic acid outside the presently claimed range.

Rule of Law

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Even if a *prima facie* case of obviousness has been established, secondary considerations such as commercial success, long felt but unsolved need, failure of others, and unexpected results may nevertheless give rise to a patentable invention. Graham v. John Deere Co., 148 U.S.P.Q. 459 (1966). Where the claimed and prior art products are substantially similar, a *prima facie* case of obviousness can also be rebutted by demonstrating that the prior art products do not possess the characteristics of the claimed invention. In re Best, 196 U.S.P.Q. 430, 433 (C.C.P.A. 1977).

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said enteric coating being hydroxypropyl methylcellulose phthalate having a degree of substitution by phthalic acid group of 20 to 27%, and said benzimidazole derivative being selected from the group consisting of omeprazole, pantoprazole, timoprazole or picoprazole.

The cited references do not teach all the claimed limitations

The references fail to teach or suggest that HPMCP having a D.S. by phthalic acid of 20 to 27% results in an enteric coating for benzimidazole derivative having unexpectedly higher residual content characteristics. Advantageously, the presently claimed enteric coating avoids the use of a water-soluble inner film for pharmaceutical formulations having benzimidazole as the active ingredient.

Lovgren et al. only teaches a pharmaceutical preparation comprising omeprazole as the core of the tablet formulation wherein the formulation has an enteric coating comprising hydroxypropylmethylcellulose phthalate. However, nothing in the reference teaches or suggests the presently claimed degree of substitution by phthalic acid group of 20 to 27%.

Similarly, Chen et al. teaches enteric coated pharmaceutical dosage forms containing omeprazole or lansoprazole as the core ingredient and the process or method for their manufacture. However, Chen et al. does not disclose the use of any other benzimidazole derivatives in the formulations.

Pierre et al. teaches water-soluble benzimidazole-containing compositions and methods for making the compositions having several derivatives as active ingredients. Although the reference teaches that enteric vehicles and compositions are particularly useful for treatment of animals suffering from severe helminthic infections of the intestinal tract and that the enteric property can be imparted to the formulation by coating said formulations with enteric coatings containing resins, waxes, synthetic polymers; nothing in the reference teaches or suggests the presently claimed degree of substitution by phthalic acid group of 20 to 27%.

In particular, orally-administered formulations of benzimidazole derivatives cannot be exposed to gastric juice due to the rapid degradation of benzimidazole in acidic environments. If the drug is prematurely exposed to stomach acids, the formulation would degrade and fail to reach the intestine. In order to reduce the formulation's acid-labile properties, a stabilizing agent such as an alkaline ingredient is usually added.

However, the addition of the alkaline agent to the enteric

coatings impairs the enteric coating which in turn reduces storage stability. Moreover, known methods require a water-soluble inner film which are unreliable and often result in inferior products which also have reduced stability. The lack of motivation to make the presently claimed invention is further evidenced by the unpredictable nature of pharmacokinetics.

Pharmacokinetics is an incredibly complex subject that is unique to each class of compound. Each pharmacokinetic study requires application of robust stochastic theory; population modeling; investigation of process and measurement noise; evaluation of alternative parameterizations of pharmacokinetic models; optimal monitoring strategies and finally clinical trials.

The unpredictable nature of pharmacokinetics and the unpredictable nature of shelf life for enteric coatings would make it extremely difficult for one of ordinary skill in the art to make the presently claimed limitation of HPMCP having a D.S. by phthalic acid of 20 to 27% without some suggestion or motivation. Clearly, in this case, one of ordinary skill would not have been provided with any guidance regarding all these various parameters for a benzimidazole formulation having increased storage stability from the cited references.

Even assuming *arguendo* that a *prima facie* exists, the § 1.132 Declaration provides statistical evidence that the presently

claimed enteric coating having a degree of substitution by a phthalic acid group of 20 to 27% (HMPCP-50) unexpectedly improves the shelf life of benzimidazole derivatives over enteric coatings having a substitution outside the claimed range such as HP-55 (27.0 to 35.0% as shown in Certificate of Analysis).

In particular, fifteen core tablets per formulation were prepared in accordance with the same procedures as Example 1 of the present specification. Samples 1 and 2 contain an omeprazole complex while Samples 3 and 4 contain a pantoprazole complex. Samples 1 and 3 have the coating composition with the ingredient HP-50 falling within the claimed limitations while Sample 2 and 4 have the coating composition with the ingredient HP-55 falling outside the presently claimed limitations. As the court stated in

The statistical grouped data of these fifteen core tablets shows that the presently claimed composition unexpectedly results in higher residual content having a degree of substitution by a phthalic acid group of 20 to 27%. In re Corkill, "a greater than expected result is an evidentiary factor pertinent to the legal conclusion of [non]obviousness". 711 F.2d 1496, 266 USPQ 1005 (Fed. Cir. 1985). The statistical analysis clearly shows that there is a reliable statistical basis for patentable distinctions between the prior art and the presently claimed formulations.

Accordingly, Applicant respectfully submits that the presently

claimed invention is unobvious over the cited references and respectfully request reconsideration and withdrawal of the rejections under 35 U.S.C. § 103.

CONCLUSION

In light of the foregoing, Applicant submits that the application is now in condition for allowance. The Examiner is therefore respectfully requested to reconsider and withdraw the rejection of the pending claims and allow the pending claims. Favorable action with an early allowance of the claims pending is earnestly solicited.

Respectfully submitted,

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